DOI:10.1111/j.1477-2574.2011.00432.x

HPB

ORIGINAL ARTICLE

Multi-institutional analysis of pancreatic adenocarcinoma demonstrating the effect of diabetes status on survival after resection

Robert M. Cannon[1], Ryan LeGrand[1], Ryaz B. Chagpar[1], Syed A. Ahmad[2], Rebecca McClaine[2], Hong Jin Kim[3], Christopher Rupp[3], Cliff S. Cho[4], Adam Brinkman[4], Sharon Weber[4], Emily R. Winslow[4], David A. Kooby[5], Carrie K. Chu[5], Charles A. Staley[5], Ian Glenn[6], William G. Hawkins[6], Alexander A. Parikh[7], Nipun B. Merchant[7], Kelly M. McMasters[1], Robert C.G. Martin[1], Glenda G. Callender[1] & Charles R. Scoggins[1]

[1]Surgery, University of Louisville, Louisville, KY, [2]Surgery, University of Cincinnati, Cincinnati, OH, [3]Surgery, University of North Carolina, Chapel Hill, NC, [4]Surgery, University of Wisconsin, Madison, WI, [5]Surgery, Emory University, Atlanta, GA, [6]Surgery, Washington University, St. Louis, MO, and [7]Surgery, Vanderbilt University, Nashville, TN, USA

Abstract

Background: The effect of diabetes on survival after resection pancreatic ductal carcinoma (PDAC) is unclear. The present study was undertaken to determine whether pre-operative diabetes has any predictive value for survival.

Methods: A retrospective review from seven centres was performed. Metabolic factors, tumour characteristics and outcomes of patients undergoing resection for PDAC were collected. Univariate and multivariable analyses were performed to determine factors associated with disease-free (DFS) and overall survival (OS).

Results: Of the 509 patients in the present study, 31.2% had diabetes. Scoring systems were devised to predict OS and DFS based on a training set ($n = 245$) and were subsequently tested on an independent set ($n = 264$). Pre-operative diabetes ($P < 0.001$), tumour size >2 cm ($P = 0.001$), metastatic nodal ratio >0.1 ($P < 0.001$) and R1 margin ($P < 0.001$) all correlated with DFS and OS on univariate analysis. Scoring systems were devised based on multivariable analysis of the above factors. Diabetes and the metastatic nodal ratio were the most important factors in each system, earning two points for OS and four points for DFS. These scoring systems significantly correlated with both DFS ($P < 0.001$) and OS ($P < 0.001$).

Conclusion: Pre-operative diabetes status provides useful information that can help to stratify patients in terms of predicted post-operative OS and DFS.

Keywords

diabetes mellitus, multivariable analysis, disease-free survival, prognostic factors, prognostic nomogram, margin, lymph node ratio

Received 14 October 2011; accepted 11 December 2011

Correspondence

Charles R. Scoggins, Division of Surgical Oncology, University of Louisville, 315 E. Broadway, Suite 303, Louisville, KY 40202, USA. Tel.: +1 502 629 3355. Fax: +1 502 629 3030. E-mail: charles.scoggins@louisville.edu

Introduction

Pancreatic adenocarcinoma (PDAC) is a devastating disease that poses significant management challenges. The incidence of PDAC continues to rise, with over 40 000 newly diagnosed patients and almost as many patient deaths in 2010. It remains the 10th most common cancer diagnosis and the 4th leading cause of cancer death in the USA.[1] Although some recent studies have reported 5-year survival rates above 20%,[2–4] the overall 5-year survival rate has changed little over the past 30 years. Although many patients present with unresectable disease, resection remains the only chance at long-term survival.

Survival after resection appears to be influenced by several independent prognostic variables including pre-operative

Presented at the Western Surgical Association Annual meeting, November 2010, Chicago, IL, USA.

comorbidities, clinicopathological characteristics, tumour biology and peri-operative complications.[5–9] Although data are conflicting, patient characteristics such as pre-existing diabetes mellitus (DM) and obesity have been shown to be associated with long-term survival after surgical resection.[10–13] Others have shown an increased risk of peri-operative complications with DM and obesity, but not survival.[14–19]

Recently, pre-existing DM has been identified as an adverse prognostic variable associated with increased mortality in various cancers, including colorectal, prostate and breast cancers.[20,21] There is a 40–65% prevalence of coexisting DM in patients with PDAC and up to 80% with some degree of impaired glucose metabolism,[22] illustrating a well-documented relationship between DM and PDAC.[23–27] Less is known, however, about the impact of pre-operative DM on post-resection outcomes, including survival. Chu *et al.*[10] in a retrospective review of 209 patients, found that pre-existing DM was independently associated with reduced survival in patients undergoing resection for PDAC. This was most pronounced in patients with new-onset DM (≤24 months), in which a larger tumour size was also noted. These findings suggest that pre-existing DM may have prognostic implications after resection for PDAC. This observation was earlier reported in a retrospective study by Sperti *et al.*,[12] in which DM was found to be independently associated with long-term survival in 113 patients who underwent resection for PDAC. Conflicting data exist,[28–30] thus, the true impact of diabetes on pancreatic cancer outcomes is not fully known.

Complete resection of all disease (R0 resection) is a core principle of surgical oncology. Numerous studies in the literature have shown that a positive resection margin (R1) in surgically treated PDAC is independently associated with poor long-term survival, and conversely, a negative margin resection has a positive impact on survival.[31–33] Some previous authors have suggested that a positive resection margin might represent a more biologically aggressive tumour and thus has significant prognostic implications on recurrence and survival.[34] Although the impact of margin status has been challenged,[35–37] most agree that efforts to obtain a negative margin probably provide benefit to the patient with PDAC. Similarly, lymph node status is important as a marker of tumour biology. The presence of nodal involvement is associated with a poor prognosis.[5,38,39] Lymph node ratio (LNR), rather than overall nodal status, has been shown to be an important prognostic factor in gastric and colon cancer.[40,41] More recently, several studies have demonstrated LNR as a valuable marker of survival after resection for PDAC.[42–46] Based on these data, it was hypothesized that survival models could be created based on pre-existing diabetes mellitus, tumour biology and resection status for patients with PDAC.

Methods

Data from seven participating centres of the Central Pancreas Consortium were used in this Institutional Review Board-approved retrospective review. The data from each centre were collected using a specified menu-driven database and then combined for analysis. Patients were included for analysis if they underwent pancreatic resection for pancreatic ductal adenocarcinoma between 1 January 2000 and 1 January 2009. Patients who had a grossly positive (R2) resection margin ($n = 9$) and those receiving neoadjuvant chemotherapy were excluded from the queried database.

Definitions

Diabetes was defined by both patient history and biochemical means, as previously described by Chu *et al.*[10] Patients with a past medical history of DM as well as those with a pre-operative fasting glucose greater than 125 mg/dl or two or more outpatient random glucose levels above 199 mg/dl were considered to be diabetic. Body mass index (BMI) was calculated and reported as kg/m^2. All pathological data, including greatest tumour diameter and lymph node status were collected as reported by each individual institution's clinical pathologists. The resection margins were defined as R0 (microscopically negative) and R1 (microscopically positive). Circumferential margins including the transection, superior mesenteric artery and retroperitoneum were examined. The R1 margin was specifically defined as less than 1 mm. The same definition for positive margins was used at all centres. Patients with an R2 margin (grossly positive) were excluded from this analysis. Pathological analysis was performed at the centre where a resection occurred, without a central review. Adjuvant chemotherapy and radiotherapy data were collected. As the purpose of this retrospective review was not to look at the impact of a specific regimen, the data were reported as categorical variables (yes/no). Disease-free survival was defined as the time interval between diagnosis of pancreatic cancer and recurrence of disease, with patients alive without disease censored at the last follow-up. Follow-up was similar at all centres, and included office visits, computed tomography imaging and CA 19-9 levels every 3 to 4 months. Recurrence was defined based on imaging and rising CA 19-9 levels. Overall survival was defined as the time interval between diagnosis and death, with censoring at the last follow-up. Post-operative deaths were defined as any death that occurred within 90 days post-operatively, regardless of admission status. Likewise, post-operative complications were counted regardless of the patient's admission status.

Statistical analyses

The cohort of interest ($n = 509$) was then randomly divided into a training set ($n = 245$) and a test set ($n = 264$). Kaplan–Meier analyses were performed on the training set in order to identify metabolic and clinicopathological factors associated with both disease-free survival (DFS) and overall survival (OS). Patients who were alive and recurrence free at the time of their last follow-up visit were censored in the analyses for DFS (right censored). Using forced entry of those covariates that attained significance in the univariate analyses ($P < 0.050$), multivariable Cox's proportional-hazards models were developed to determine factors

Table 1 Clinicopathological characteristics of training (n = 245) and test set (n = 264) populations

Factor	Training set n = 245	Test set n = 264	P-value
	n (%)	n (%)	
Age ≥65	137 (55.9)	149 (56.4)	0.929
Male	115 (46.9)	134 (50.8)	0.425
Pre-operative DM	78 (31.8)	81 (30.7)	0.848
BMI ≥ 30	55 (22.4)	53 (20.1)	0.517
≥1 other comorbidity (cardiac, renal and pulmonary)	61 (24.9)	82 (31.1)	0.139
Type of resection			0.091
Whipple	199 (81.2)	190 (72.0)	
Whipple with portal or superior mesenteric vein resection	21 (8.6)	32 (12.1)	
Distal pancreatectomy	20 (8.2)	37 (14.0)	
Central pancreatectomy	0 (0)	1 (0.4)	
Subtotal pancreatectomy	4 (1.6)	3 (1.1)	
Adjuvant chemotherapy	144 (58.8)	141 (53.4)	0.272
Adjuvant radiotherapy	82 (33.5)	64 (24.2)	0.073
Peri-operative complication	136 (55.5)	152 (57.6)	0.655
Histological grade			0.934
Well-differentiated	28 (11.4)	30 (11.4)	
Moderately-differentiated	141 (57.6)	158 (59.8)	
Poorly differentiated/anaplastic	72 (29.4)	75 (28.4)	
R1 margin	61 (24.9)	66 (25.0)	0.979
Nodal ratio >0.1	110 (44.9)	130 (49.2)	0.373
Tumour size ≥2 cm	213 (86.9)	229 (86.7)	0.895

DM, diabetes mellitus; BMI, body mass index.

that were independently associated with survival. Two simple integer-based scoring systems that could be used to model OS and DFS were then created based on the beta-coefficients of our multivariable analyses. The scores were then tested for their association with survival in the test set using log-rank tests. An asymptotically unbiased concordance index, which differs from the Harrell's c-statistic in that it is robust to the degree of censoring, was used to determine the overall discriminatory ability of our OS scoring system, as well as that of the currently proposed AJCC system (7th edition) for patients diagnosed with resectable disease (stages I to IIB).[47] It should be noted that the patient cohort used to derive and test the OS and DFS scores included the 209 patients from Chu's prior study concerning the significance of diabetes to survival,[10] and these patients would have been divided between the training and validation sets via the process of random sampling described above.

Results

Clinicopathological data

In all, 509 patients from seven academic medical centres underwent a resection for PDAC from 1 January 2000 to 1 January 1 2009. The median age of the entire cohort was 67.0 years [interquartile range (IQR) = 58.0–74.0], with a median follow-up time of 14.5 months. At the end of the study 334 patients were deceased. There were 159 (31.2%) patients who had diabetes as a pre-operatively identified comorbidity, of which 68 (43%) were insulin dependent. The median BMI was 26 kg/m^2 (IQR = 23–29 kg/m^2). The clinicopathological features of patients in both the training and test sets are indicated in Table 1.

Operative and pathological data

For the entire cohort studied, the majority of patients were treated with a pancreaticoduodenectomy (n = 442, 86.8%), of whom 53 (10.4%) required vascular resection to achieve tumour extirpation. The remaining individuals underwent distal (n = 57, 11.2%), central (n = 1, 0.2%) or a subtotal pancreatectomy (n = 7, 1.4%). The median operative blood loss was 500 ml (range 50–5650 ml) and 41.8% (n = 213) of patients received a blood component transfusion peri-operatively. The post-operative complication rate was 56.6% (n = 288), with a 90-day mortality of 5.5% (n = 28). The most common type of complication was infectious, representing 44.2% (127 patients) of all complications. Eight per cent (n = 41) of patients developed a pancreatic fistula.

While most patients had an R0 resection, 127 (25.0%) tumour specimens had microscopically positive margins. The median tumour size was 3.1 cm (IQR = 2.5–4.0 cm), and nodal metastases were present in 57% (n = 290) of patients. Of the patients with tumour-positive lymph nodes, the median lymph node (LN) ratio

Table 2 Univariate analyses of factors associated with OS and DFS in the training set (n = 245)

Factor	Median OS	*P*-value	Median DFS	*P*-value
	Months (95% CI)		(Months)	
Pre-operative DM	14.8 (14.2–15.4)	<0.001	10.2 (9.0–11.4)	<0.001
Tumour size ≥ 2 cm	17.0 (15.1–18.9)	0.010	12.4 (10.8–14.0)	0.018
R1 margin	14.6 (12.2–17.0)	<0.001	8.8 (7.4–10.2)	<0.001
Nodal ratio > 0.1	15.8 (14.3–17.3)	<0.001	11.0 (9.8–12.2)	<0.001
BMI ≥ 30 kg/m^2	15.8 (13.7–17.9)	0.143	10.5 (9.5–11.5)	0.164

OS, overall survival; DFS, disease-free survival; CI, confidence interval; SD, standard deviation; DM, diabetes mellitus; BMI, body mass index.

Table 3 Cox multivariate analysis of factors associated with OS and DFS in the training set

Factor	OS			DFS		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Pre-operative DM	1.99	1.40–2.82	<0.001	1.67	1.32–2.11	<0.001
Nodal ratio > 0.1	1.96	1.41–2.72	<0.001	1.84	1.47–2.31	<0.001
Tumour size ≥ 2 cm	1.80	1.06–3.02	0.030	1.32	0.95–1.84	0.093
R1 margin	1.62	1.13–2.32	0.008	1.28	1.01–1.64	0.044

OS, overall survival; DFS, disease-free survival; DM, diabetes mellitus; HR, hazard ratio; CI, confidence interval.

Table 4 Median survival times for OS and DFS scores in training (n = 245) and test (n = 264) sets

OS score			DFS score		
Points	Training set	Test set	Points	Training set	Test set
	Median OS months (95% CI)	Median OS months (95% CI)		Median DFS months (95% CI)	Median DFS months (95% CI)
0–1	34.3 (29.5–40.9)	31.0 (26.9–35.1)	0–2	26.0 (16.3–35.7)	15.8 (12.9–20.2)
2–3	17.4 (17.2–22.8)	17.5 (15.7–19.1)	3–5	12.6 (10.7–14.5)	10.8 (8.9–12.7)
4–6	14.6 (11.6–16.3)	14.2 (13.5–15.6)	6–8	8.8 (6.3–11.3)	8.6 (6.2–11.0)

OS, overall survival; DFS, disease-free survival; DM, diabetes mellitus; CI, confidence interval.

was 0.25 (IQR = 0.1–0.44) and the median number of positive LN was 2 (IQR = 1–4). The median number of nodes harvested was 10 (IQR = 6–16). The degree of tumour differentiation was as follows: 11% (n = 58) well differentiated, 59% (n = 299) moderately differentiated and 29% (n = 147) poorly differentiated. Twenty-eight per cent of patients (n = 146) received adjuvant chemo-radiotherapy, whereas an additional 27% (n = 139) received adjuvant chemotherapy only. The breakdown of the above factors in the test set and training set are presented in Table 1.

Scoring systems

Univariate analysis of OS and DFS revealed pre-operative DM, a tumour size ≥2 cm, lymph node ratio (LNR) > 0.1 and positive resection margin were all associated with a poorer DFS and OS (Table 2). Pre-operative DM, LNR > 0.1, tumour size ≥2 cm and an R1 resection all retained significance in the multivariate analysis of OS (Table 3). Each of these factors, with the exception of tumour size ≥2 cm, was also independently associated with DFS (Table 3). The median OS and DFS in the training set was 18.3 (IQR 11.2–30.0) months, and 13.2 (IQR 8.0–26.8) months, respectively.

Scoring systems to model OS and DFS were then created based on the beta coefficients from these multivariable analyses. For the OS score, tumour size ≥2 cm and R1 resection were each assigned one point, whereas two points were assigned for each of pre-operative DM or LNR > 0.1, respectively. A similar integer-based scoring system was designed for DFS (R1 margin = 1 point, tumor size ≥2 cm = 2 points, pre-operative DM or LNR > 0.1 = 4 points each).

The OS score was significantly associated with survival in the training set (Table 4) When applied to the test set, the OS score was similarly associated with survival, and adequate discrimination was observed between each of the point groups (P < 0.001 for all pair-wise comparisons). A comparable stratification of median survival time by point-group was also observed for the DFS score in both the training and test sets, although with poorer discrimination between point groups 3–5 and 6–8 (P < 0.050 for all pair-wise comparisons).

A comparison between the current AJCC staging system (7th edition) and the proposed OS score is presented in Fig. 1. While the AJCC system adequately discriminated between stages IIB vs.

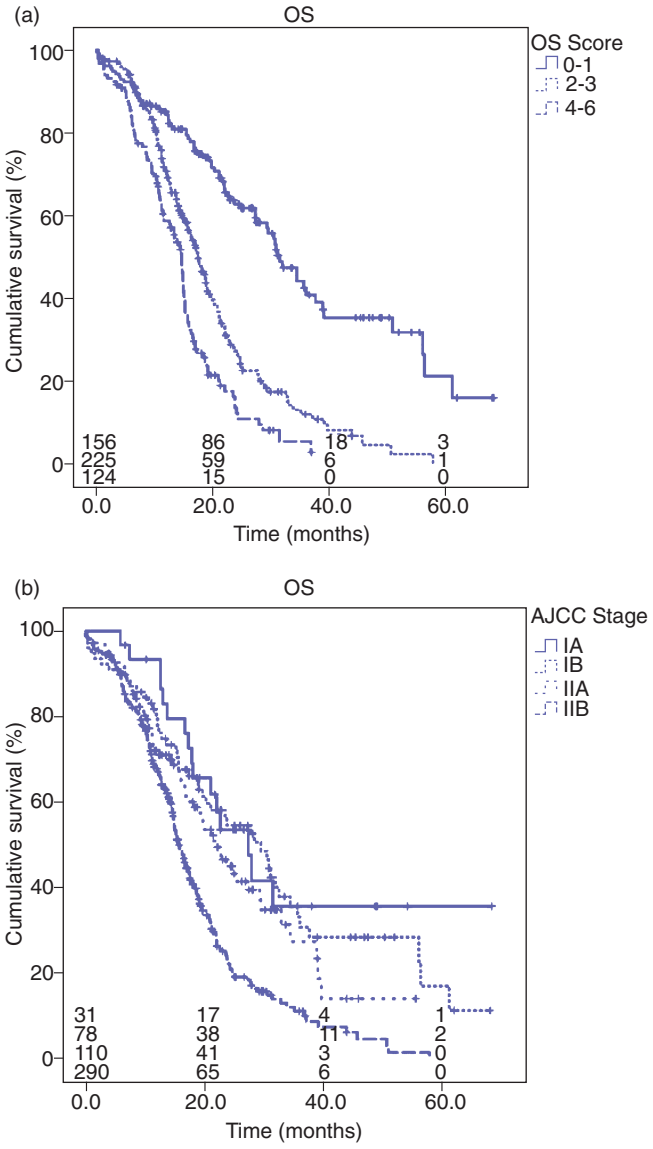

Figure 1 Overall survival of patients with resectable pancreatic ductal adenocarcinoma stratified by: (a) overall survival (OS) score and (b) AJCC staging system. Numbers at risk are along the *x*-axis

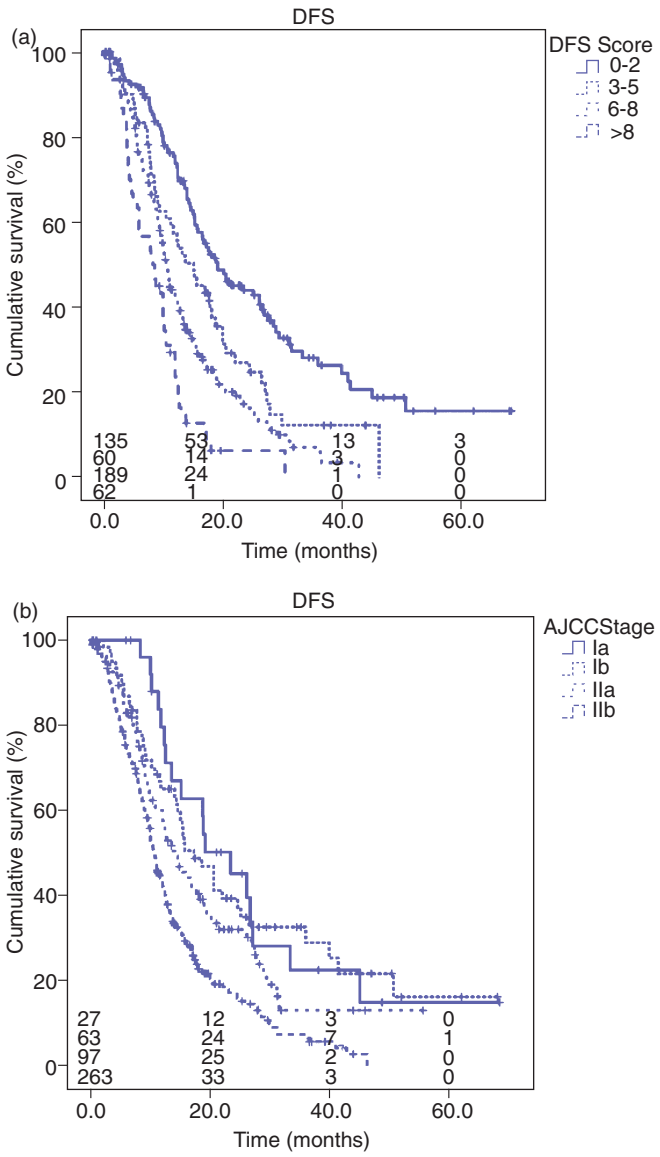

Figure 2 Disease-free survival (DFS) of patients with resectable pancreatic ductal adenocarcinoma stratified by: (a) DFS score, (b) AJCC staging system. Numbers at risk are along the *x*-axis

IA, IB and IIA, respectively ($P < 0.001$ for all pairwise comparisons), poor discrimination was observed between all other stages. Overall, the AJCC system exhibited moderate discriminatory ability with a concordance index of 0.58 ± 0.02. The OS score, conversely, demonstrated adequate interstage discrimination between all point groups ($P < 0.001$ for all interstage comparisons), and superior performance overall, with a concordance index of 0.64 ± 0.02. The components of the OS score responsible for increased concordance over the AJCC system were diabetes status and margin. The concordance for the OS score without diabetes and margin status decreased by 0.06, essentially reducing the discriminatory ability to that of the AJCC system. Similar results were found for the comparison of the DFS score and the AJCC stage (Fig 2).

Discussion

In spite of few encouraging reports in recent literature,[2–4] the prognosis for patients diagnosed with PDAC continues to be poor and a minority of patients present with resectable disease. For those patients that have undergone resection, prognosis is dictated by tumour biology, clinicopathological characteristics, surgical and peri-operative factors, and molecular genetics. Several of

these variables have been shown to be associated with recurrence and survival.[5–9] The AJCC staging system[48] is the most widely used tool for estimating prognosis. More recently, the Memorial Sloan Kettering group has developed and validated a prognostic nomogram,[49] which integrates additional prognostic factors in an attempt to better model disease-specific survival for individual patients. This system incorporates 18 different variables, and the authors report a concordance index of 0.64. Although not all variables were available to allow direct comparison of the proposed nomogram to the MSKCC nomogram, the identical reported concordance index suggests that the two systems are similar in their predictive ability. The currently proposed scoring system has the advantage of increased ease of use as a result of lesser variables included.

On multivariable analysis, pre-operative DM, tumour size ≥2 cm, LNR > 0.1 and a positive resection margin were all identified to be independently associated with OS, whereas DM, LNR > 0.1 and a positive resection margin were independently associated with DFS. These prognostic factors were then used to create novel scoring systems that could predict survival outcomes. Pre-operative DM was found to be an independent prognostic factor for both DFS and OS in the current analysis. This is consistent with recent literature examining the relationship between DM and PDAC. Sperti *et al.*,[12] in a retrospective study of 113 patients who underwent surgical resection of PDAC found DM to be an independently associated with long-term survival on multivariable analysis. Chu *et al.*[10] showed that DM was also associated with increased tumour size and that new-onset DM patients (<24 months) exhibited this relationship most strongly. One-third of the current patient population was found to be diabetic, which is similar to that reported by others.[28,50,51] Reasons for the poorer survival seen with diabetes may be related to increased circulating levels of insulin in these patients, as malignant tumours often over express receptors for insulin and insulin-like growth factor 1.[52,53] Thus, the higher insulin levels seen in diabetic patients may serve as a trophic factor for malignancy. The other factors found to be significant in the present study (lymph node involvement, tumour size and resction margin), are already well described in the literature.[9,30–33,36–39,42–46,54–57]

Additional investigators may continue with our proposed scoring models but allow for other variables. For example, those who had received neoadjuvant chemotherapy were excluded from our cohort. Lim *et al.*,[54] while recognizing the prognostic value of biological characteristics, suggests that the most powerful determinant of post-operative survival for the post-resection patient is adjuvant chemoradiation therapy. Others have found adjuvant therapies to be significant, as well.[9,54,55] Contrarily, Schnelldorfer *et al.*[39] and others[56,57] have not found adjuvant chemoradiation therapy to have a significant influence on long-term survival. There was not a significant effect for adjuvant chemo/radiotherapy in the present study. However, this study was not designed to properly evaluate the effects of adjuvant therapy, so this conclusion should be interrupted with caution.

In terms of application of how this system may be applied, consider a hypothetical patient with a 3-cm tumour that was excised to microscopically negative (R0) margins. The patient had pre-operative diabetes, and there was no metastatic or nodal disease. Under the AJCC system this patient would be placed in category IB, with a median OS of roughly 30 months based on Kaplan–Meier curves obtained by applying the AJCC system to the data set under analysis. Using the currently proposed OS scoring system, the patient would have three points, with an expected median OS of only 17 months, which is closer to that of stage IIB patients. Thus application of the proposed scoring system, with its increased discriminatory ability, more correctly places the patient in a survival category that is one stage higher. Such information is valuable not only for patient counselling and follow-up planning, but for future research use as well in stratifying patients by survival risk.

There have already been a number of schemes devised for predicting survival or PDAC as outlined above. The novel value of the present study, therefore, is not necessarily that the proposed scoring system is dramatically better then what is already available, but rather, that this represents the largest study to clearly define the substantial negative impact that diabetes has on survival. Upon multivariable analysis, the hazard ratio for OS associated with diabetes was higher than that for margin status, metastatic lymph node ratio, or tumor size. For DFS, the hazard ratio associated with diabetes was higher than those for tumor size or margin status, although less important than metastatic nodal ratio. Thus, not only is diabetes a significant predictor of survival, but the present study is the first to demonstrate that it may have a more important impact than more traditional risk factors. The reasons for this survival impact are subjects for future study.

Pancreatic adenocarcinoma continues to be a difficult disease to diagnose and treat. In spite advances in surgical techniques and peri-operative care, consistent long-term survival remains elusive. Significant improvements in long-term survival will probably come from the development of effective systemic therapies and that this should be the goal of future research. It is the authors' hope that the development of scoring systems such as the one offered herein prove useful for clinicians and researchers who deal with pancreatic adenocarcinoma. Limitations of the present study include its retrospective design and a lack of central pathological review. The present study was confined to specialized centres and thus may not be representative of the population of patients with a pancreatic ductal adenocarcinoma as a whole.

Conflicts of interest

None declared.

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